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Synthesis and antiviral activity of camphor-based 1,3-thiazolidin-4-one and thiazole derivatives as *Orthopoxvirus*-reproduction inhibitors†

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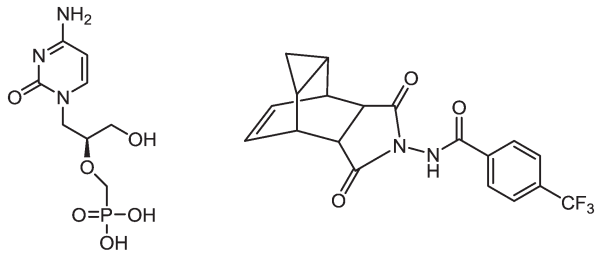
The *Orthopoxvirus* genus belongs to the Poxviridae family and includes variola virus (smallpox), cowpox virus, monkeypox virus and vaccinia virus (VV). Smallpox is considered one of the great epidemic disease scourges in human history. It has currently been eradicated; however, it remains a considerable threat as a biowarfare or bioterrorist weapon. The poxvirus, VV, serves as a model virus from which new antiviral therapies against *Orthopoxviruses* can be identified. Here, a series of nitrogen–sulphur containing heterocycles such as 1,3-thiazolidin-4-one and thiazoles containing a 1,7,7-trimethylbicyclo[2.2.1]heptan scaffold were synthesized and screened for their antiviral activity. The bioassay results showed that the **4b**, **4c** and **4e** thiazoles, which contained a substituted benzene ring, were able to inhibit VV reproduction with IC_{50} values in the 2.4–3.7 micromolar range whilst exhibiting moderate cytotoxicity. Among the thiazolidin-4-one derivatives, compound **8b**, which contained a 4-methylbenzylidene group, displayed good inhibitory activity (IC_{50} = 9.5 μM) and moderate toxicity.

Introduction

The genus *Orthopoxvirus* belongs to the Poxviridae family and is a group of large complex double-stranded DNA viruses that includes variola virus, cowpox virus, monkeypox virus and vaccinia virus (VV). Variola is the causative agent of smallpox. In 1980, the World Health Organization declared this disease to be eradicated worldwide and vaccination was discontinued. Thus most individuals have never been vaccinated, and those who were vaccinated over 20 years ago have presumably lost their immunity. Although variola virus no longer circulates amongst the human population, there has recently been heightened concern that smallpox may be used as a bioterrorist agent.[1] There are currently no licensed pharmacological agents for the treatment of poxvirus infection; however, a number of antiviral substances (*i.e.* thiosemicarbazones, nucleoside and nucleotide analogues, interferon, interferon inducers and other compounds) have been evaluated for their efficacy against *Orthopoxviruses*.[2] Experiments in mice and lower primates showed promising antiviral activities of Cidofovir, a nucleoside analogue used in US clinics in the treatment of herpes virus infections,[3] and Tecovirimat (ST-246), which was developed by SIGA Technologies as a drug for the postexposure treatment of *Orthopoxvirus* disease[4] (Fig. 1). However, considering the increasing threat of *Orthopoxvirus*-related infections, it is necessary to identify novel chemical compounds with different mechanisms of action to create a new generation of antiviral agents.

Heterocyclic compounds are key structures in drug discovery and design due to their different biological properties. Ring synthesis by cyclisation of opportune linear compounds is one of the most common methods in which heterocyclic compounds are prepared. Thiosemicarbazones are particularly suitable substrates for the preparation of nitrogen–sulphur containing heterocycles such as 1,3-thiazolidin-4-one and thiazoles.[5] It is worth noting that some



Cidofovir ST-246 (Tecovirimat)

Fig. 1 Chemical structure of inhibitors of *Orthopoxvirus* replication.

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thiosemicarbazone compounds have prophylactic activity against smallpox disease and therapeutic activity against VV infections.[6] Thus, thiosemicarbazone compounds is perspective scaffold for create *Orthopoxvirus* inhibitors.

On the other hand, 1,7,7-trimethylbicyclo[2.2.1]heptan scaffolds are structural units in numerous bioactive compounds such as camphor and borneol that possess different biological activity; for example, antimicrobial,[7] antiviral,[8–10] antioxidant,[11] analgesic[12] and receptor antagonist.[13] The structural features of this system such as *gem*-dimethyl group and conformationally rigid bicycle can modify the rotational barriers and stabilise a bioactive conformation and provide favourable van der Waals interactions with the binding site of the target protein.[14] Moreover, previously we have shown that combination of a saturated N-heterocycle, such as morpholine or 4-methylpiperidine, and a 1,7,7-trimethylbicyclo[2.2.1]heptan scaffold was favourable for antiviral activity against *Orthopoxviruses*.[15] In the present work, to create novel inhibitors of *Orthopoxviruses*, we utilised the molecular hybridisation approach which involves coupling of the pharmacophoric (+)-camphors scaffold and thiosemicarbazone moieties. The design strategy is shown in Fig. 2. It was important for us to identify the influence type of heterocyclic ring and their substituents.

Results and discussion

Chemistry

The key starting material, thiosemicarbazone **1**, was obtained by heating thiosemicarbazide with (+)-camphor in the presence of a few drops of sulfuric acid. Synthesis of the 2,4-disubstituted thiazoles included the two steps depicted in Scheme 1. In the first step, the required 1-aryl-2-bromoethanones **3a–g** were prepared from the reaction of acetophenones **2a–g** with *N*-bromosuccinimide (NBS). Several experiments were performed to optimise the reaction conditions for bromination, including using NBS in the presence of different catalysts such as montmorillonite K-10 clay and *p*-toluenesulfonic acid (Ts-OH). The NBS–Ts-OH system was shown to be optimum. Finally, camphor thiosemicarbazone **1** was reacted with different 2-bromoacetophenones to convert it into 2,4-disubstituted thiazoles **4a–g** (Scheme 1).

Thiosemicarbazone **1** reacted with cyclisation reagents (*i.e.* ethyl-2-bromoacetate) to give a substituted thiazolidin-4-one

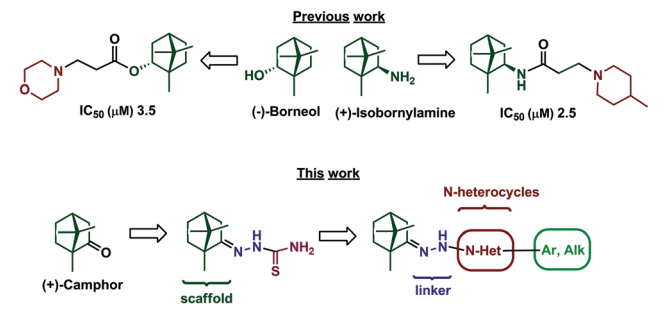
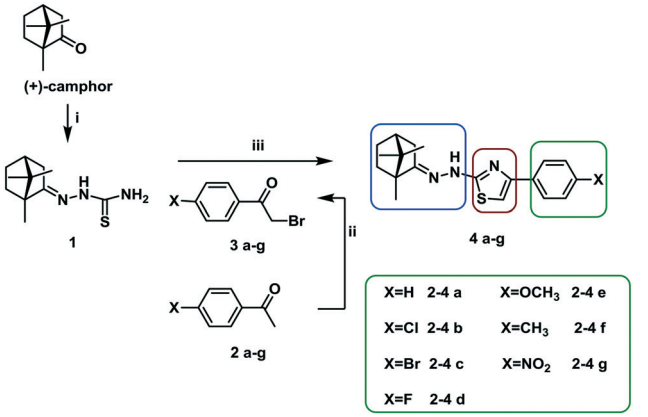
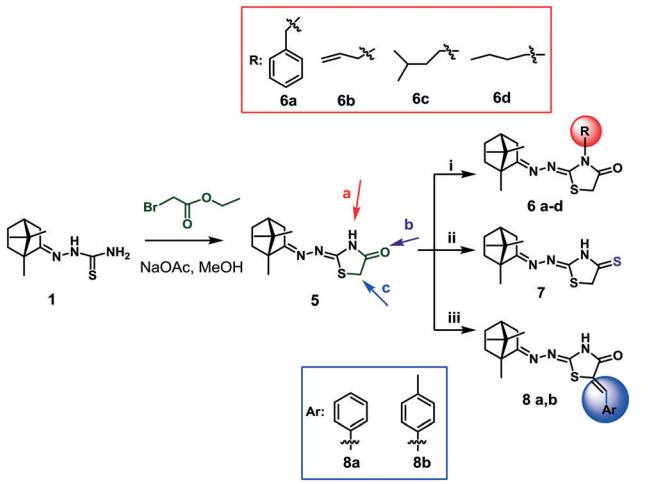


Fig. 2 Design strategy for new compounds.



Scheme 1 Reagents and conditions: (i) $NH_2NHCSNH_2$, EtOH, H_2SO_4 and reflux; (ii) NBS, Ts-OH and stirring at room temperature; (iii) corresponding 1-aryl-2-bromoethanones **3a–g**, $CHCl_3$: EtOH (2 : 1) and reflux.

derivative **5**. The design strategy was aimed at derivatising this scaffold and included three synthetic reactions: alkylation at the nitrogen atom, substitution of the carbonyl group for thiocarbonyl and a condensation reaction (Scheme 2). Alkylation of 1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylidene(hydrazono)thiazolidin-4-one **5** by corresponding bromides in the presence of anhydrous K_2CO_3 in dry acetone produced the **6a–d** derivatives. Moreover enhancement of the thiazolidinonelactame activity was attempted. One obvious possibility was to convert the 4-thiazolidinone **5** into a 4-thiazolidinethione **7**, which is possible using Lawesson's reagent. Finally, to probe the importance of the C-5 position of the thiazolidin-4-one cycle, analogues bearing aromatic groups were synthesised. As shown in Scheme 2, the reaction of compound **5** with aromatic aldehydes in the presence of sodium acetate in glacial acetic acid produced the



Scheme 2 Reagents and conditions: (i) corresponding bromide, K_2CO_3, dry acetone, stirring at slight hitting; (ii) Lawesson's reagent, toluene, reflux; (iii) aromatic aldehyde, NaOAc, CH_3COOH, reflux.

corresponding 5-(substituted)-2-(((1*R*,4*R*)-1,7,7-trimethylbicyclo-[2.2.1]heptan-2-ylidene)hydrazinyl)thiazol-4(5*H*)-one **8a–b**.

Compounds **4a**, **4c–4g** were synthesised previously, and their antifungal and antibacterial activities were studied.[16] Compounds **4b**, **5**, **6a–d**, **7** and **8a–b** were not described previously, therefore investigation of the antiviral activity of the obtained compounds was conducted for the first time.

Biological activity

Structure–activity relationship

The antiviral activity and cytotoxicity of the synthesised derivatives against VV were evaluated using an adapted method.[17] The commercially available agent, Cidofovir, was used as a positive control, and the results are shown in Table 1. The synthesised compounds can be divided into two main clusters according to the type of derivatisation of camphor thiosemicarbazone **1**: (a) those derivatives containing thiazole (*e.g.* **4a–g**) and (b) those with a 1,3-thiazolidin-4-one ring (*e.g.* **5**, **6a–d** and **8a–b**).

The starting 2-(1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylidene)hydrazinecarbothioamide **1** exhibited moderate antiviral activity and low toxicity, giving a selectivity index (SI) result of 13. The thiazole containing an unsubstituted benzene ring **4a** showed a low IC_{50} value of 3.2 μM and a high toxicity TC_{50} value of 13.9 μM. Adding electro-withdrawing lipophilic substitutions, such as halogens and nitro groups, reduced the toxicity in comparison with the unsubstituted benzene ring. These findings were evidenced by the TC_{50} values of the corresponding substitutions: *p*-chloro compound **4b** TC_{50} = 64.1 μM, *p*-bromo compound **4c** TC_{50} = 77.1 μM, *p*-fluoro compound **4d** TC_{50} = 175.8 μM and *p*-nitro compound **4 g** TC_{50} = 261.0 μM.

Table 1 Antiviral activity of target derivatives against VV

Compound	TC_{50}[a] (μM) $M \pm I_{95}$, $n = 3$[e]	IC_{50}[b] (μM) $M \pm I_{95}$, $n = 3$	SI[c]
1	224.8 ± 25.4	17.7 ± 0.4	13
4a	13.9 ± 4.6	3.2 ± 1.1	—
4b	64.1 ± 5.8	2.7 ± 0.5	24
4c	77.1 ± 9.4	2.4 ± 1.2	32
4d	175.8 ± 6.9	NA[d]	—
4e	93.6 ± 20.6	3.7 ± 1.4	26
4f	13.7 ± 7.4	4.5 ± 1.1	3
4g	261.0 ± 20.4	NA	—
5	305.2 ± 74.3	NA	—
6a	287.8 ± 51.0	NA	—
6b	163.9 ± 30.0	14.4 ± 0.7	11
6c	37.5 ± 8.5	NA	—
6d	25.2 ± 3.4	3.2 ± 1.7	8
7	17.5 ± 2.3	3.3 ± 0.3	5
8a	14.5 ± 4.4	5.2 ± 1.0	3
8b	120.5 ± 4.7	9.5 ± 2.5	13
Cidofovir	475.3 ± 74.9	40.01 ± 2.8	12

[a] TC_{50}: 50% toxicity concentration, at which 50% of cells in uninfected monolayers are destroyed. [b] IC_{50}: 50% inhibitory concentration, at which 50% of cells in infected monolayers are preserved. [c] SI: selectivity index, ratio of TC_{50} to IC_{50}. [d] NA: no activity. [e] *M* – mean value; I_{95} – 95% confidence interval; *n* – the number of repeats of measurement of TC_{50} and IC_{50}.

Moreover, chloro- and bromo-substituted compounds **4b** and **4c** displayed potent inhibitory activities that resulted in high SI values of 24 and 32, respectively. Compounds **4e** and **4f**, which contained electron-donating methoxy and methyl groups in the *para* position, displayed the same level of potency with IC_{50} values of 3.7 and 4.5 μM, respectively. However, the methoxy oxygen played an important role in toxicity, as this group remarkably reduced the toxicity (compound **4e** TC_{50} = 93.6 μM and compound **4f** TC_{50} = 13.7 μM).

The results showed that amongst the thiazolidin-4-one derivatives, the starting substance 2-((*E*)-2-((1*R*,4*R*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylidene)hydrazinyl)thiazol-4(5*H*)-one **5** did not show antiviral activity. Improved inhibitory potency was achieved with alkylation at the nitrogen atom. Two compounds exhibited good inhibitory activity, namely compounds **6b** (IC_{50} = 14.4 μM) and **6d** (IC_{50} = 3.2 μM) which had allyl and *n*-butyl substituents, respectively. The presence of an aromatic fragment in thiazolidin-4-one **6a** significantly reduced the toxicity but did not show inhibitory activity. The isopentane substituent in compound **6c** exhibited no antiviral activity and increased the toxicity more than six-fold in comparison with the starting thiazolidin-4-one **5**.

The effect of condensing the aromatic ring at position C-5 of the thiazolidin-4-one cycle was also considered. Derivative **8b** containing a 4-methylbenzylidene group displayed good inhibitory activity (IC_{50} = 9.5 μM) together with a moderate toxicity (TC_{50} = 120.5 μM). Meanwhile, the **8a** analogue containing a benzylidene group showed a low inhibitory activity (IC_{50} = 5.2 μM) and a high toxicity (TC_{50} = 14.5 μM). Replacing the 4-thiazolidinone heterocyclic with the 4-thiazolidinethione contributed to the antiviral activity whilst significantly increasing toxicity. This was revealed by comparing the starting compound **5** (no activity; TC_{50} = 305.2 μM) with derivative **7** (IC_{50} = 3.3 μM; TC_{50}= 17.5 μM).

Conclusion

Thus, 2-(1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylidene)-hydrazinecarbothioamide **1** could be used as a scaffold to construct heterocyclic systems containing 1,3-thiazolidin-4-one and thiazole rings. Some synthesised heterocycles had promising antiviral activity towards VV. The cyclisation of camphor thiosemicarbazone **1** to different thiazoles led to a reduced IC_{50} value in most cases; however, this was also accompanied by increased toxicity. Any modification to 2-((*E*)-2-((1*R*,4*R*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylidene)hydrazinyl)thiazol-4(5*H*)-one **5** caused a significant improvement in antiviral activity and increased toxicity; however, this was not the case with derivative **6a**, where adding a benzene substituent at the nitrogen atom reduced the toxicity. These findings show that 2-(1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylidene)-hydrazinecarbothioamide is a promising scaffold to develop new inhibitors of VV. These preliminary results are promising and indicate the need for subsequent the determination of an antiviral target, the testing of promising agents against variola virus and the experiments using animal models.

Experimental

Reagents and solvents were purchased from commercial suppliers and used as received. Dry solvents were obtained according to the standard procedures. Optical rotation: PolAAr 3005 spectrometer; $CHCl_3$ soln. ^1H and ^{13}C NMR spectra were recorded with a Bruker AV-300 (^1H: 300.13 MHz, ^{13}C: 75.47 MHz), AV-400 (^1H: 400.13 MHz, ^{13}C: 100.78 MHz) in $CDCl_3$; chemical shifts δ in ppm relative to residual [$\delta(CHCl_3)$ 7.24, $\delta(CDCl_3)$ 76.90]. Spin multiplicities are given as s (singlet), d (doublet), t (triplet) and m (multiplet) as well as b (broad). Coupling constants (J) are given in hertz. HR-MS: DFS Thermo Scientific spectrometer in full scan mode (15–500 m/z, 70 eV electron impact ionization, direct sample administration) and Agilent 7200 Quadrupole Time-of-Flight GC/MS system. Elemental analysis was carried out using a Euro EA 3000 C,H,N,S-analyzer. Analysis of Cl was carried out by the mercurimetric titration method. The purity of the target compounds was determined by gas chromatography methods. All of the target compounds reported in this paper have a purity of no less than 96%. Column chromatography (CC) was performed on silica gel (60–200 l, Macherey-Nagel). Numeration of atoms in the compounds is given for assigning the signals in the NMR spectra and does not coincide with that for the names according to the nomenclature of compounds (see ESI†). Specific rotation is expressed as (deg ml) (g dm)$^{-1}$; concentration is expressed as (g) (100 ml)$^{-1}$.

Synthesis

Synthesis of 2-((1*R*,4*R*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylidene)hydrazinecarbothioamide 1. A solution of thiosemicarbazide (0.01 mol) in ethanol was added to a solution of (+)-camphor (0.01 mol) in ethanol and several drops of H_2SO_4. The mixture was heated at reflux in 10 h and evaporation under reduced pressure gave the corresponding thiosemicarbazone. This compound was recrystallized from ethanol to give white solid: yield 74%; mp 167.1 °C; The spectral characteristics of compound **1** coincide with the literature data.[18]

General procedure for the synthesis of thiazoles 4a–g

Example for 4-phenyl-2-(2-((1*R*,4*R*)-1,7,7-trimethylbicyclo-[2.2.1]heptan-2-ylidene)hydrazinyl)thiazole 4a. A mixture of *N*-bromosuccinimide (1 g, 6.6 mmol) and *p*-toluenesulfonic acid (0.2 g, 1.3 mmol) was added to acetophenone and stirred at room temperature for 5 h. The mixture was washed with brine (2 × 10 mL), dried over Na_2SO_4, and concentrated to give the 2-bromo-1-phenylethanone. To a solution of brominated ketone (1.3 g, 6.5 mmol) in the mixture ethanol : $CHCl_3$ (1 : 2) (15 mL) was added thiosemicarbazone **1** (1.5 g, 6.5 mmol). The reaction was refluxed for 24 h. Next, the reaction mixture was washed with brine (10 mL) and saturated solution of $NaHCO_3$, dried over Na_2SO_4, and concentrated to give the thiazole **4a** as a brown solid: yield: 71% mp = 254.7 °C; NMR ^1H (400 MHz, $CDCl_3$, δ, ppm, J Hz^{-1}): 0.72 (3H, s, Me-9), 0.89 (3H, s, Me-10), 0.97 (3H, s, Me-8), 1.17–1.27 (1H, m, H-4endo), 1.35–1.44 (1H, m, H-5endo), 1.71–1.80 (1H, m, H-5exo), 1.80–1.91 (1H, m, H-4exo), 2.04 (1H, dd, $J_{3,2exo} = J_{3,4exo}$ = 4.2, H-3), 2.12 (1H, d, ^2J = 17.5, H-2endo), 2.59 (1H, m, H-2exo), 6.69 (1H, s, H-12), 7.34–7.45 (3H, H-19, H-17, H-18), 7.70 (2H, d, J = 7.2, H-15,H-16). NMR ^{13}C (100 MHz, $CDCl_3$, δ, ppm): 174.8 s (C-11), 168.9 s (C-1), 140.3 s (C-13), 129.9 d (C-19), 129.2 d (C-17, C-18), 127.4 s (C-14), 125.3 d (C-15, C-16), 100.6 d (C-12), 53.2 s (C-6), 48.2 s (C-7), 43.7 d (C-3), 35.9 t (C-2), 32.2 t (C-5), 26.6 t (C-4), 19.2 q (C-10), 18.3 q (C-9), 13.9 q (C-17), 10.5 q (C-8). $[\alpha]_D^{25}$ = −46 ($CHCl_3$, c = 0.5). Anal. calcd for $C_{19}H_{23}N_3S$: C 70.11%, H 7.12%; N 12.91%; S 9.85%; found: C 69.94%, H 7.08%, N 12.39%, S 9.72%.

4-(4-Chlorophenyl)-2-(2-((1*R*,4*R*)-1,7,7-trimethylbicyclo-[2.2.1]heptan-2-ylidene)hydrazinyl)thiazole 4b. The compound **4b** was prepared by reaction of compound **1** and 2-bromo-1-(4-chlorophenyl)ethanone according to the general procedure. The product was purified by CC (eluent: hexane–ethyl acetate) to give the thiazole **4b** as a brown crystals: yield 41%; mp = 73.4 °C; NMR ^1H (400 MHz, $CDCl_3$, δ, ppm, J Hz^{-1}): 0.75 (3H, s, Me-9), 0.93 (3H, s, Me-10), 1.04 (3H, s, Me-8), 1.14–1.22 (1H, m, H-4endo), 1.39–1.47 (1H, m, H-5endo), 1.69–1.78 (1H, m, H-5exo), 1.78–1.92 (2H, m, H-4exo, H-2endo), 1.99 (1H, t, $J_{3,2exo} = J_{3,4exo}$ = 4.4, H-3), 2.35 (1H, m, H-2exo), 6.80 (1H, s, H-12), 7.29–7.34 (2H, m, H-17, H-18), 7.67–7.72 (2H, m, H-15,H-16). NMR ^{13}C (100 MHz, CDCl3, δ, ppm): 169.9 s (C-11), 164.6 s (C-1), 149.8 s (C-13), 133.4 s (C-19), 133.1 s (C-14), 128.6 d (C-17, C-18), 127.0 d (C-15, C-16), 103.4 d (C-12), 52.4 s (C-6), 47.9 s (C-7), 43.9 d (C-3), 33.5 t (C-2), 32.5 t (C-5), 27.1 t (C-4), 19.4 q (C-10), 18.5 q (C-9), 10.1 q (C-8). $[\alpha]_D^{27}$ = −15.4 ($CHCl_3$, c = 0.4). Anal. calcd for $C_{19}H_{22}ClN_3S$: C 63.40%, H 6.16%, Cl 9.85%, N 11.67%, S 8.91%; found: C 62.28%, H 6.11%, Cl 9.96%, N 11.26%, S 9.65%.

4-(4-Bromophenyl)-2-(2-((1*R*,4*R*)-1,7,7-trimethylbicyclo-[2.2.1]heptan-2-ylidene)hydrazinyl)thiazole 4c. The compound **4c** was prepared by reaction of compound 1 and 2-bromo-1-(4-bromophenyl)ethanone according to the general procedure. The product was purified by CC (eluent: hexane–ethyl acetate) to give the thiazole **4c** as a brown crystals: yield 43%; mp = 78.7 °C; NMR ^1H (400 MHz, $CDCl_3$, δ, ppm, J Hz^{-1}): 0.73 (3H, s, Me-9), 0.92 (3H, s, Me-10), 1.03 (3H, s, Me-8), 1.11–1.19 (1H, m, H-4endo), 1.38–1.46 (1H, m, H-5endo), 1.68–1.77 (1H, m, H-5exo), 1.77–1.89 (2H, m, H-4exo, H-2endo), 1.97 (1H, t, $J_{3,2exo} = J_{3,4exo}$ = 4.4, H-3), 2.34 (1H, m, H-2exo), 6.80 (1H, s, H-12), 7.44–7.49 (2H, m, H-17, H-18), 7.60–7.65 (2H, m, H-15,H-16). NMR ^{13}C (100 MHz, $CDCl_3$, δ, ppm): 169.7 s (C-11), 164.8 s (C-1), 149.6 s (C-13), 133.6 s (C-14), 131.5 d (C-17, C-18), 127.3 d (C-15, C-16), 121.4 s (C-19), 103.5 d (C-12), 52.5 s (C-6), 48.0 s (C-7), 44.0 d (C-3), 33.6 t (C-2), 32.5 t (C-5), 27.1 t (C-4), 19.4 q (C-10), 18.5 q (C-9), 10.9 q (C-8). $[\alpha]_D^{25}$ = −47 ($CHCl_3$, c = 0.5). HRMS: m/z calcd. for $C_{19}H_{22}N_3Br_1S_1$: 403.0712. Found: 403.0714.

4-(4-Fluorophenyl)-2-(2-((1*R*,4*R*)-1,7,7-trimethylbicyclo-[2.2.1]heptan-2-ylidene)hydrazinyl)thiazole 4d. The compound **4d** was prepared by reaction of compound **1** and

2-bromo-1-(4-fluorophenyl)ethanone according to the general procedure. The product was purified by CC (eluent: hexane–ethyl acetate) to give the thiazole **4d** as a brown solid: yield 34%; NMR ^{1}H (400 MHz, $CDCl_3$, δ, ppm, J Hz^{-1}): 0.71 (3H, s, Me-9), 0.91 (3H, s, Me-10), 1.03 (3H, s, Me-8), 1.05–1.12 (1H, m, H-4endo), 1.35–1.44 (1H, m, H-5endo), 1.66–1.85 (3H, m, H-5exo, H-4exo, H-2endo), 1.93 (1H, t, $J_{3,2exo} = J_{3,4exo} = 4.4$, H-3), 2.29 (1H, m, H-2exo), 6.73 (1H, s, H-12), 6.99–7.07 (2H, m, H-17, H-18), 7.68–7.76 (2H, m, H-15, H-16). NMR ^{13}C (100 MHz, $CDCl_3$, δ, ppm): 170.8 s (C-11), 166.1 s (C-1), 166.0 d (J_{C-F} = 257.4 Hz, C-19), 133.4 d (J_{C-F} = 9.2 Hz, C-15, C-16), 127.9 d (J_{C-F} = 8.4 Hz, C-19), 125.4 s (C-13), 116.1 d (J_{C-F} = 21.6 Hz, C-17, C-18), 100.6 d (C-12), 53.7 s (C-6), 48.2 s (C-7), 43.8 d (C-3), 36.8 t (C-2), 32.5 t (C-5), 27.0 t (C-4), 19.5 q (C-10), 18.6 q (C-9), 10.8 q (C-8). $[\alpha]_D^{28}$ = 30.5 ($CHCl_3$, c = 0.7). HRMS: m/z calcd. for $C_{19}H_{22}N_3F_1S_1$: 343.1513. Found: 343.1519.

4-(4-Methoxyphenyl)-2-(2-((1*R*,4*R*)-1,7,7-trimethylbicyclo-[2.2.1]heptan-2-ylidene)hydrazinyl)thiazole 4e. The compound **4e** was prepared by reaction of compound **1** and 2-bromo-1-(4-methoxyphenyl)ethanone according to the general procedure. The product was purified by CC (eluent: hexane–ethyl acetate) to give the thiazole **4e** as a brown solid: yield 71%; NMR ^{1}H (400 MHz, $CDCl_3$, δ, ppm, J Hz^{-1}): 0.73 (3H, s, Me-9), 0.91 (3H, s, Me-10), 1.04 (3H, s, Me-8), 1.07–1.15 (1H, m, H-4endo), 1.37–1.45 (1H, m, H-5endo), 1.66–1.86 (3H, m, H-5exo, H-4exo, H-2endo), 1.95 (1H, t, $J_{3,2exo} = J_{3,4exo} = 4.3$, H-3), 2.31 (1H, m, H-2exo), 3.80 (3H, s, Me-20), 6.67 (1H, s, H-12), 6.86–6.91 (2H, m, H-17, H-18), 7.66–7.71 (2H, m, H-15, H-16), 8.34 (1H, br.s., N–H). NMR ^{13}C (100 MHz, $CDCl_3$, δ, ppm): 169.8 s (C-11), 164.5 s (C-1), 159.1 s (C-19), 150.6 s (C-13), 133.1 s (C-14), 127.0 d (C-15, C-16), 113.8 d (C-17, C-18), 101.2 d (C-12), 55.2 q (C-20), 52.4 s (C-6), 48.0 s (C-7), 44.0 d (C-3), 33.5 t (C-2), 32.5 t (C-5), 27.2 t (C-4), 19.4 q (C-10), 18.5 q (C-9), 10.9 q (C-8). $[\alpha]_D^{28}$ = −49 ($CHCl_3$, c = 0.6). Anal. calcd for $C_{20}H_{25}N_3OS$: C 67.57%, H 7.09%, N 11.82%, O 4.50%, S 9.02%; found: C 67.36%, H 7.09%, N 11.31%, O 4.74%, S 8.95%.

4-Tolyl-2-(2-((1*R*,4*R*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylidene)hydrazinyl)thiazole 4f. The compound **4f** was prepared by reaction of compound **1** and 2-bromo-1-tolylethanone according to the general procedure. The product was purified by CC (eluent: hexane–ethyl acetate) to give the thiazole 8f as a brown crystals: yield 56%; mp = 121.6 °C; NMR ^{1}H (400 MHz, $CDCl_3$, δ, ppm, J Hz^{-1}): 0.73 (3H, s, Me-9), 0.91 (3H, s, Me-10), 1.04 (3H, s, Me-8), 1.09–1.17 (1H, m, H-4endo), 1.38–1.46 (1H, m, H-5endo), 1.67–1.87 (3H, m, H-5exo, H-4exo, H-2endo), 1.95 (1H, t, $J_{3,2exo} = J_{3,4exo} = 4.3$, H-3), 2.32 (1H, m, H-2exo), 2.33 (3H, s, Me-20), 6.75 (1H, s, H-12), 7.13–7.19 (2H, m, H-17, H-18), 7.62–7.67 (2H, m, H-15, H-16), 8.24 (1H, br.s., N–H). NMR ^{13}C (100 MHz, $CDCl_3$, δ, ppm): 169.4 s (C-11), 163.8 s (C-1), 151.1 s (C-13), 137.1 s (C-19), 132.2 s (C-14), 129.0 d (C-17, C-18), 125.6 d (C-15, C-16), 102.2 d (C-12), 52.3 s (C-6), 47.9 s (C-7), 44.0 d (C-3), 33.3 t (C-2), 32.5 t (C-5), 27.1 t (C-4), 21.0 q (C-20), 19.4 q (C-10), 18.5 q (C-9), 10.9 q (C-8). $[\alpha]_D^{28}$ = −70.4 ($CHCl_3$, c = 0.5). HRMS: m/z calcd. for $C_{20}H_{25}N_3S_1$: 339.1764. Found: 339.1772.

4-(4-Nitrophenyl)-2-(2-((1*R*,4*R*)-1,7,7-trimethylbicyclo[2.2.1]-heptan-2-ylidene)hydrazinyl)thiazole 4g. The compound **4g** was prepared by reaction of compound **1** and 2-bromo-1-(4-nitrophenyl)ethanone according to the general procedure. The product was purified by CC (eluent: hexane–ethyl acetate) to give the thiazole **4g** as a yellow powder: yield 38%; mp = 202.4 °C; NMR ^{1}H (400 MHz, $CDCl_3$, δ, ppm, J Hz^{-1}): 0.76 (3H, s, Me-9), 0.94 (3H, s, Me-10), 1.05 (3H, s, Me-8), 1.16–1.23 (1H, m, H-4endo), 1.39–1.49 (1H, m, H-5endo), 1.71–1.79 (1H, m, H-5exo), 1.81–1.92 (2H, m, H-4exo, H-2endo), 2.02 (1H, t, $J_{3,2exo} = J_{3,4exo} = 4.3$, H-3), 2.38 (1H, m, H-2exo), 7.04 (1H, s, H-12), 7.88–7.94 (2H, m, H-16, H-15), 8.12 (1H, br.s., N–H), 8.19–8.24 (2H, m, H-17, H-18). NMR ^{13}C (100 MHz, CDCl3, δ, ppm): 169.4 s (C-11), 164.7 s (C-1), 148.4 s (C-13), 146.4 s (C-19), 140.4 s (C-14), 125.8 d (C-15, C-16), 123.6 d (C-17, C-18), 106.8 d (C-12), 52.2 s (C-6), 47.7 s (C-7), 43.7 d (C-3), 33.1 t (C-2), 32.2 t (C-5), 26.9 t (C-4), 19.1 q (C-10), 18.2 q (C-9), 10.6 q (C-8). $[\alpha]_D^{28}$ = −50.8 ($CHCl_3$, c = 0.3). Anal. calcd for $C_{19}H_{22}N_4O_2S$: C 61.60%, H 5.99%, N 15.12%, O 8.64%, S 8.66%; found: C 61.72%, H 5.98%, N 15.15%, O 8.77%, S, 8.97%.

Synthesis of 2-(((1*R*,4*R*)-1,7,7-trimethylbicyclo[2.2.1]-heptan-2-ylidene)hydrazinyl)thiazol-4(5*H*)-one5. Thiosemicarbazone **1** (0.036 mol), anhydrous sodium acetate (0.5 mol), and 30 ml methanol were added to a round bottom flask under magnetic stirring and slightly warmed for 10–15 min. Then, ethyl 2-bromoacetate (0.5 mol) was added, and the reaction was kept under reflux heating for 12 h. After cooling to room temperature, the organic layer was washed with brine and extracted with $CHCl_3$. The combined organic phase was dried over anhydrous Na_2SO_4 and the solvent was removed. The product was purified by recrystallization from ethanol to give white crystals: yield 59%; mp 191.0–192.5 °C; NMR ^{1}H (400 MHz, $CDCl_3$, δ, ppm, J Hz^{-1}): 0.79 (3H, s, Me-9), 0.92 (3H, s, Me-10), 1.02 (3H, s, Me-8), 1.19–1.27 (1H, m, H-4endo), 1.38–1.46 (1H, m, H-5endo), 1.67–1.87 (2H, m, H-5exo, H-4exo), 1.89 (1H, t, $J_{3,2exo} = J_{3,4exo} = 4.3$, H-3), 2.11 (1H, d, ^2J = 18.1, H-2endo), 2.61 (1H, m, H-2exo), 3.68 (2H, s, H-12). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 180.1 s (C-1), 173.7 s (C-11), 53.1 s (C-6), 47.9 s (C-7), 43.9 d (C-3), 35.7 t (C-2), 33.0 t (C-5), 32.7 t (C-12), 27.0 t (C-4), 19.4 q (C-10), 18.6 q (C-9), 11.0 q (C-8). $[\alpha]_D^{24}$ = −57 ($CHCl_3$, c = 0.8). HRMS: m/z calcd. for $C_{13}H_{19}ON_3S$: 265.1243. Found: 265.1242.

General procedure for the synthesis of thiazolidinones 6a–d

3-Benzyl-2-(((1*R*,4*R*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylidene)hydrazono)thiazolidin-4-one 6a. To a stirred solution of 4-oxothiazolidine **5** (2 mmol) in 10 ml of anhydrous acetone was added (bromomethyl)benzene (2 mmol) and K_2CO_3 (5 mmol). The mixture was allowed to stirring at slight hitting for 8 hour. The mixture was then washed with brine and extracted with $CHCl_3$, dried (Na_2SO_4), filtered and concentrated. The crude product was purified by silica gel CC (eluent: hexane–ethyl acetate) to give white crystals: yield 64%; mp 114.2–114.8 °C; NMR ^{1}H (400 MHz, $CDCl_3$, δ, ppm, J

Hz^{-1}): 0.77 (3H, s, Me-9), 0.92 (3H, s, Me-10), 1.03 (3H, s, Me-8), 1.17–1.26 (1H, m, H-4endo), 1.38–1.47 (1H, m, H-5endo), 1.67–1.76 (1H, m, H-5exo), 1.78–1.88 (1H, m, H-4exo), 1.91 (1H, t, $J_{3,2exo} = J_{3,4exo}$ = 4.3, H-3), 2.04 (1H, d, ^2J = 18.1, H-2endo), 2.54 (1H, m, H-2exo), 3.69 (2H, s, H-12), 4.91 (2H, s, H-14), 7.22–7.32 (3H, m, H-16, H-17, H-20), 7.43–7.48 (2H, m, H-18, H-19). NMR ^{13}C (100 MHz, $CDCl_3$, δ, ppm): 180.7 s (C-1), 171.7 s (C-13), 158.5 s (C-11), 135.7 s (C-15), 129.0 d (C-18, C-19), 128.1 d (C-16, C-17), 127.6 d (C-20), 52.6 s (C-6), 47.8 s (C-7), 46.3 t (C-14), 43.7 d (C-3), 36.0 t (C-2), 32.5 t (C-5), 32.1 t (C-12), 27.1 t (C-4), 19.5 q (C-10), 18.6 q (C-9), 10.9 q (C-8). $[\alpha]_D^{28}$ = −49.6 ($CHCl_3$, c = 0.6). HRMS: m/z calcd. for $C_{20}H_{25}ON_3S$: 355.1713. Found: 355.1715.

3-Allyl-2-(((1*R*,4*R*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylidene)hydrazono)thiazolidin-4-one 6b. The compound **6b** was prepared by reaction of compound **5** and allyl bromide according to the general procedure. The product was purified by CC (eluent: hexane–ethyl acetate) to give a yellow oil: yield 62%. NMR ^{1}H (400 MHz, $CDCl_3$, δ, ppm, J Hz^{-1}): 0.77 (3H, s, Me-9), 0.92 (3H, s, Me-10), 1.03 (3H, s, Me-8), 1.17–1.25 (1H, m, H-4endo), 1.38–1.47 (1H, m, H-5endo), 1.67–1.76 (1H, m, H-5exo), 1.77–1.86 (1H, m, H-4exo), 1.88 (1H, t, $J_{3,2exo} = J_{3,4exo}$ = 4.3, H-3), 2.03 (1H, d, ^2J = 18.1, H-2endo), 2.51 (1H, m, H-2exo), 3.70 (2H, s, H-12), 4.33 (2H, m, H-14), 5.15–5.29 (2H, m, H-16), 5.78–5.89 (1H, m, H-15). NMR ^{13}C (100 MHz, $CDCl_3$, δ, ppm): 180.8 s (C-1), 171.5 s (C-13), 157.9 s (C-11), 130.4 d (C-15), 118.5 t (C-16), 52.7 s (C-6), 47.9 s (C-7), 45.2 t (C-14), 43.7 d (C-3), 35.9 t (C-2), 32.5 t (C-5), 32.2 t (C-12), 27.1 t (C-4), 19.5 q (C-10), 18.6 q (C-9), 10.9 q (C-8). $[\alpha]_D^{24}$ = −64.6 ($CHCl_3$, c = 0.6). HRMS: m/z calcd. for $C_{16}H_{23}O_1N_3S_1$: 305.1556. Found: 305.1561.

3-Isopentyl-2-(((1*R*,4*R*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylidene)hydrazono)thiazolidin-4-one 6c. The compound **6c** was prepared by reaction of compound **5** and 1-bromo-3-methylbutane according to the general procedure. The product was purified by CC (eluent: hexane–ethyl acetate) to give a yellow oil: yield 57%. NMR ^{1}H (400 MHz, $CDCl_3$, δ, ppm, J Hz^{-1}): 0.77 (3H, s, Me-9), 0.92 (3H, s, Me-10), 0.91 (6H, d, J = 6.3, Me-17, Me-18), 1.03 (3H, s, Me-8), 1.17–1.26 (1H, m, H-4endo), 1.39–1.47 (1H, m, H-5endo), 1.49–1.61 (3H, m, H-15, H-16), 1.67–1.76 (1H, m, H-5exo), 1.78–1.86 (1H, m, H-4exo), 1.88 (1H, t, $J_{3,2exo} = J_{3,4exo}$ = 4.3, H-3), 2.05 (1H, d, ^2J = 18.1, H-2endo), 2.52 (1H, m, H-2exo), 3.66 (2H, s, H-12), 3.74 (2H, t, J = 7.3, H-14). NMR ^{13}C (100 MHz, $CDCl_3$, δ, ppm): 180.5 s (C-1), 171.8 s (C-13), 158.7 s (C-11), 52.7 s (C-6), 47.9 s (C-7), 43.7 d (C-3), 41.7 t (C-14), 35.8 t (C-2), 35.5 t (C-15), 32.5 t (C-5), 32.2 t (C-12), 27.1 t (C-4), 25.8 d (C-16), 22.3 q (C-17, C-18), 19.5 q (C-10), 18.6 q (C-9), 10.9 q (C-8). $[\alpha]_D^{24}$ = −67.5 ($CHCl_3$, c = 0.4). HRMS: m/z calcd. for $C_{18}H_{29}ON_3{}^{32}S$: 335.2026. Found: 335.2027.

3-Butyl-2-(((1*R*,4*R*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylidene)hydrazono)thiazolidin-4-one 6d. The compound **6d** was prepared by reaction of compound **5** and 1-bromobutane according to the general procedure. The product was purified by CC (eluent: hexane–ethyl acetate) to give a pale yellow powder: yield 58%; mp 69.5–75.3 °C; NMR ^{1}H (400 MHz, $CDCl_3$, δ, ppm, J Hz^{-1}): 0.77 (3H, s, Me-9), 0.92 (3H, s, Me-10), 0.91 (3H, q, J = 7.5, Me-17), 1.03 (3H, s, Me-8), 1.18–1.26 (1H, m, H-4endo), 1.26–1.37 (2H, hex, J = 7.5, H-16), 1.40–1.48 (1H, m, H-5endo), 1.59–1.68 (2H, m, H-15), 1.68–1.76 (1H, m, H-5exo), 1.78–1.87 (1H, m, H-4exo), 1.89 (1H, t, $J_{3,2exo} = J_{3,4exo}$ = 4.3, H-3), 2.05 (1H, d, ^2J = 18.1, H-2endo), 2.53 (1H, m, H-2exo), 3.67 (2H, s, H-12), 3.74 (2H, t, J = 7.4, H-14). NMR ^{13}C (100 MHz, $CDCl_3$, δ, ppm): 180.5 s (C-1), 171.9 s (C-13), 158.6 s (C-11), 52.7 s (C-6), 47.9 s (C-7), 43.7 d (C-3), 43.0 t (C-14), 35.8 t (C-2), 32.6 t (C-5), 32.2 t (C-12), 28.8 t (C-15), 27.2 t (C-4), 19.9 t (C-16), 19.5 q (C-10), 18.6 q (C-9), 13.6 q (C-17), 10.9 q (C-8). $[\alpha]_D^{27}$ = −59.8 ($CHCl_3$, c = 1.2). HRMS: m/z calcd. for $C_{17}H_{27}ON_3{}^{32}S$: 321.1869. Found: 321.1869.

2-(((1*R*,4*R*)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-ylidene)-hydrazinyl)thiazole-4(5*H*)-thione7. A one-necked flask, equipped with a magnetic stirrer bar was charged with thiazolidinone **5** (1.0 equiv.), Lawesson's reagent (0.6 equiv.), and toluene. The reaction was refluxed overnight. To the mixture was added saturated solution of $Na_2S_2O_3$ (20 ml), then the mixture was extracted with EtOAc. The organic layer was washed successively with saturated solution of $NaHCO_3$ and brine, and dried over anhydrous sodium sulfate. The product was purified by CC (eluent: hexane–ethyl acetate) to give a brown crystals: yield 51%. NMR ^{1}H (400 MHz, $CDCl_3$, δ, ppm, J Hz^{-1}): 0.77 (3H, s, Me-9), 0.92 (3H, s, Me-10), 1.03 (3H, s, Me-8), 1.22–1.30 (1H, m, H-4endo), 1.42–1.52 (1H, m, H-5endo), 1.68–1.77 (1H, m, H-5exo), 1.77–1.88 (1H, m, H-4exo), 1.90 (1H, t, $J_{3,2exo} = J_{3,4exo}$ = 4.3, H-3), 2.14 (1H, d, ^2J = 18.1, H-2endo), 2.54 (1H, m, H-2exo), 4.23 (2H, s, H-12). NMR ^{13}C (100 MHz, $CDCl_3$, δ, ppm): 202.2 s (C-13), 181.4 s (C-1), 164.0 s (C-11), 52.8 s (C-6), 47.7 s (C-7), 44.2 t (C-12), 43.5 d (C-3), 35.5 t (C-2), 32.1 t (C-5), 26.6 t (C-4), 19.2 q (C-10), 18.3 q (C-9), 10.6 q (C-8). $[\alpha]_D^{26}$ = 312 ($CHCl_3$, c = 0.14). HRMS: m/z calcd. for $C_{13}H_{19}N_3{}^{32}S_2$: 281.1015. Found: 281.1011.

5-Benzylidene-2-(((1*R*,4*R*)-1,7,7-trimethylbicyclo[2.2.1]-heptan-2-ylidene)hydrazinyl)thiazol-4(5*H*)-one 8a. To a solution of thiazolidin-4-one (1 equiv.) **5** in glacial acetic acid aromatic aldehyde (1.5 equiv.) and NaOAc (1 equiv.) were added. The solution was refluxed till completion of the reaction monitored by TLC. The reaction mixture was allowed to cool at room temperature, water was added and the product was extracted into $CHCl_3$. The organic layer was washed with brine (10 mL) and saturated solution of $NaHCO_3$, dried over Na_2SO_4, and concentrated to give the compound **8a** as white powder; yield 52%; mp = 227.9; NMR ^{1}H (400 MHz, $CDCl_3$, δ, ppm, J Hz^{-1}): 0.84 (3H, s, Me-9), 0.94 (3H, s, Me-10), 1.11 (3H, s, Me-8), 1.22–1.32 (1H, m, H-4endo), 1.43–1.53 (1H, m, H-5endo), 1.72–1.90 (2H, m, H-5exo, H-4exo), 1.94 (1H, t, $J_{3,2exo} = J_{3,4exo}$ = 4.3, H-3), 2.20 (1H, d, ^2J = 18.1, H-2endo), 2.38 (3H, s, Me-21), 2.70 (1H, m, H-2exo), 7.26 (2H, d, J = 8.7, H-18, H-19), 7.45 (2H, d, J = 8.7, H-16, H-17), 7.64 (1H, s, H-14). NMR ^{13}C (100 MHz, $CDCl_3$, δ, ppm): 181.5 s (C-1), 168.0 s (C-13), 157.2 s (C-11), 134.1 s (C-15), 130.9 d (C-14), 130.3 d (C-16, C-17), 129.9 d (C-20), 129.2 d (C-18, C-19), 123.0 s (C-12), 53.6 s (C-6), 48.3 s (C-7), 44.2 d (C-3), 36.3 t (C-2), 33.0 t (C-5), 27.4 t (C-4), 19.9 q (C-10), 19.0 q (C-9), 11.5 q (C-8).

$[\alpha]_D^{30}$ = −89.7 ($CHCl_3$, c = 0.7). HRMS: m/z calcd. for $C_{20}H_{23}O_1N_3S_1$: 353.1556. Found: 353.1557.

5-(4-Methylbenzylidene)-2-(((1*R*,4*R*)-1,7,7-trimethylbicyclo-[2.2.1]heptan-2-ylidene)hydrazinyl)thiazol-4(5*H*)-one 8b. Compound **8b** was prepared by a procedure analogous to compound **8a**. Yellow crystals: yield 45%; mp = 227.9; NMR ^1H (400 MHz, $CDCl_3$, δ, ppm, J Hz^{-1}): 0.84 (3H, s, Me-9), 0.94 (3H, s, Me-10), 1.11 (3H, s, Me-8), 1.22–1.32 (1H, m, H-4endo), 1.43–1.53 (1H, m, H-5endo), 1.72–1.90 (2H, m, H-5exo, H-4exo), 1.94 (1H, t, $J_{3,2exo} = J_{3,4exo}$ = 4.3, H-3), 2.20 (1H, d, ^2J = 18.1, H-2endo), 2.38 (3H, s, Me-21), 2.70 (1H, m, H-2exo), 7.26 (2H, d, J = 8.7, H-18, H-19), 7.45 (2H, d, J = 8.7, H-16, H-17), 7.64 (1H, s, H-14). NMR ^{13}C (100 MHz, $CDCl_3$, δ, ppm): 180.9 s (C-1), 167.8 s (C-13), 157.1 s (C-11), 140.1 s (C-15), 131.1 s (C-20), 130.7 d (C-14), 130.0 d (C-16, C-17), 129.6 d (C-18, C-19), 121.5 s (C-12), 53.2 s (C-6), 47.9 s (C-7), 43.9 d (C-3), 36.0 t (C-2), 32.7 t (C-5), 27.1 t (C-4), 21.4 q (C-21), 19.5 q (C-10), 18.6 q (C-9), 11.1 q (C-8). $[\alpha]_D^{24}$ = −99.2 ($CHCl_3$, c = 0.6). HRMS: m/z calcd. for $C_{21}H_{25}O_1N_3S_1$: 367.1713. Found: 367.1711.

Screening for cytotoxicity and antiviral activity

A typical representative of *Orthopoxviruses*, the vaccinia virus (strain Copenhagen), obtained from the State Collection of Virus Infection and Rickettsiosis Agents of VECTOR was used in the work. The virus was grown in Vero cell culture. The virus concentration in the culture liquid was determined by plaque titration in Vero cell culture, calculated and expressed in decimal logarithms of plaque-forming units in 1 ml ($\log_{10}$ PFU ml^{-1}). The concentration of the virus in the samples used in the work was from 5.6 to 6.1 $\log_{10}$ PFU ml^{-1}. The series of virus with the indicated titer was stored and used at work at −70 °C.

The antiviral efficacy of the compounds was evaluated as follows. In wells of 96-well plates containing a monolayer of Vero cells in 100 μl of DMEM medium with 2% fetal serum, 50 μl of serial dilutions of the test compounds were first introduced and then 50 μl of dilution of *Orthopoxvirus* at a dose of 1000 PFU per well. The toxicity of the compounds was determined by the Vero cell death caused by the drug in the wells of the plate, to which the virus was not introduced. Monolayers of cells were used as controls in the wells of the plate, into which virus without compounds (virus control) and monolayers of cells in wells into which neither the virus nor the compound was introduced (cell culture control) were introduced. After incubation for 4 days, the monolayer of cells was stained with vital dye neutral red for 2 hours. After removing the dye and washing the wells from its unbound fraction, a lysis buffer was added. The amount of dye adsorbed by the living cells of the monolayer was evaluated by optical density (OD), which is an indication of the number of cells undisturbed under the influence of the virus in a monolayer. The OD was measured on an Emax spectrophotometer (Molecular Devices, USA) at a wavelength of 490 nm. Results were processed using the Soft Max Pro 4.0 program, which computed the 50% toxic concentration (TC_{50} in μM) and 50% inhibitory concentration (IC_{50} in μM). The selectivity index (SI) was determined as SI = TC_{50}/IC_{50} using the corresponding concentrations.

Conflicts of interest

There are no conflicts to declare.

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